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Early Electroencephalography for Outcome Prediction of Postanoxic Coma: A Prospective Cohort Study

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Objective: To provide evidence that early electroencephalography (EEG) allows for reliable prediction of poor or good outcome after cardiac arrest.

Methods: In a 5-center prospective cohort study, we included consecutive, comatose survivors of cardiac arrest. Continuous EEG recordings were started as soon as possible and continued up to 5 days. Five-minute EEG epochs were assessed by 2 reviewers, independently, at 8 predefined time points from 6 hours to 5 days after cardiac arrest, blinded for patients' actual condition, treatment, and outcome. EEG patterns were categorized as generalized suppression (<10 μV), synchronous patterns with ≥50% suppression, continuous, or other. Outcome at 6 months was categorized as good (Cerebral Performance Category [CPC] = 1–2) or poor (CPC = 3–5).

Results: We included 850 patients, of whom 46% had a good outcome. Generalized suppression and synchronous patterns with ≥50% suppression predicted poor outcome without false positives at ≥6 hours after cardiac arrest. Their summed sensitivity was 0.47 (95% confidence interval [CI] = 0.42–0.51) at 12 hours and 0.30 (95% CI = 0.26–0.33) at 24 hours after cardiac arrest, with specificity of 1.00 (95% CI = 0.99–1.00) at both time points. At 36 hours or later, sensitivity for poor outcome was ≤0.22. Continuous EEG patterns at 12 hours predicted good outcome, with sensitivity of 0.50 (95% CI = 0.46–0.55) and specificity of 0.91 (95% CI = 0.88–0.93); at 24 hours or later, specificity for the prediction of good outcome was <0.90.

Interpretation: EEG allows for reliable prediction of poor outcome after cardiac arrest, with maximum sensitivity in the first 24 hours. Continuous EEG patterns at 12 hours after cardiac arrest are associated with good recovery.

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Postanoxic brain injury is among the most frequent causes of coma in the intensive care unit (ICU). The chance of recovery of consciousness and independence in activities of daily living within 6 months is approximately 50%.[1,2] Early prediction of recovery perspectives may guide decisions on continuation or withdrawal of life-sustaining

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treatment. Current guidelines focus on prediction of poor outcome and recommend the use of absent pupillary light and corneal reflexes or bilaterally absent somatosensory evoked potential (SSEP) responses for decisions on treatment withdrawal, given their low false-positive rates.[3,4] However, of these predictors, sensitivity to identification of patients with a poor outcome is limited, ranging from 13 to 48%, and their reliability is insufficient during hypothermia and sedation.[5]

Recent studies have shown that the electroencephalogram (EEG) contains valuable information to assist in prediction of poor and good outcome after cardiac arrest. This information could only be extracted when appreciating EEG patterns in relation to the time since cardiac arrest. The best discrimination between patients with good and poor outcomes was possible with EEG recorded within the first 24 hours after cardiac arrest, despite treatment with targeted temperature management and sedation.[1,6] The prognostic value of the EEG seemed lower after the first 24 hours and remained unclear for the period beyond 72 hours.[1,7–11] Several previous studies did not explicitly acknowledge the time dependency of postanoxic EEG patterns.[2,12–15]

In all studies on early EEG for prognostication after cardiac arrest, a continuous, normal amplitude background pattern at 12 hours was associated with a good neurological outcome.[1,7,8] Otherwise, isoelectric or low-voltage patterns at 24 hours after cardiac arrest were invariably associated with poor outcome.[1,7] Time-independent predictors of poor outcome were generalized periodic discharges on a suppressed background[7,9,16] and burst suppression with identical bursts.[1,7,8] Results on the prognostic value of other burst-suppression patterns are conflicting.[1,7–10]

With this study, we validate the use of early EEG for outcome prediction of coma after cardiac arrest in a multicenter prospective cohort study. To improve predictive values and applicability, we use recent findings to refine EEG categories[1] and align classification with standardized critical care EEG terminology.[17] We determine optimal timing and assess the additional yield of EEG recordings beyond 24 hours.

Patients and Methods

Study Design and Participants

This is a prospective cohort study on intensive care units of 5 teaching hospitals in the Netherlands (Medical Spectrum Twente, Rijnstate Hospital, St Antonius Hospital, University Medical Center Groningen, and VieCuri Medical Center). Consecutive, adult, comatose (Glasgow Coma Scale <8 or suspected in sedated patients) patients after cardiac arrest were included. EEG recordings were started as soon as possible after admission, preferably within 12 hours after cardiac arrest. For practical reasons, EEG recordings were only started between 8 AM and 8 PM at each center, and not during weekend days in 1 center. EEG recordings were continued until patients were awake or died, with a maximum of 5 days. Some of the EEG data from 2 centers were used in previous publications on visual or quantitative EEG analyses.[1,18,19] In the participating hospitals, continuous EEG monitoring was considered standard care for patients after cardiac arrest. The Medical Research Ethics Committee Twente waived the need for informed consent for the EEG monitoring. Informed consent was obtained from surviving patients at time of follow-up.

Standard of Care

Patients were treated according to standard protocols for comatose patients after cardiac arrest. A target temperature of 33°C or 36°C was induced as soon as possible after arrival at the ICU and maintained for 24 hours. Patients received propofol, midazolam, or both for sedation, and morphine, fentanyl, or remifentanil for analgesia. At 1 center, the majority of patients were anesthetized with sevoflurane instead of propofol or midazolam. Doses of anesthetic drugs were titrated to the minimum required to maintain adequate sedation. Because all centers participated in the TELSTAR trial on treatment of status epilepticus after cardiac arrest,[20] their use of antiepileptic drugs was aligned. For patients who did not participate in TELSTAR, standard of care was to withhold treatment of electrographic status epilepticus.

Decisions of Withdrawal of Life-Sustaining Treatment

Withdrawal of treatment was considered ≥72 hours after cardiac arrest, never during hypothermia, and off sedation. For decisions on withdrawal of care, all participating centers followed recommendations by the Netherlands Society of Neurology. These are in line with international recommendations[3] and based on bilateral absence of the SSEP, absent or extensor motor responses, and absence of brainstem reflexes. Decisions on treatment withdrawal were sporadically taken between 48 and 72 hours in case of absent brainstem reflexes or SSEP responses. EEG recordings were used for early detection and treatment of electrographic seizure activity. None of the centers has recommendations to withdraw care based solely on early EEG findings (<72 hours after cardiac arrest).

Data Collection and Analysis

Continuous EEG recordings were started as soon as possible after arrival at the ICU and continued up to 5 days, or until discharge from the ICU. Twenty-one electrodes were placed on the scalp according to the international 10–20 system. Visual analysis of EEG data was prespecified and performed offline, after the recordings. A computer algorithm selected 5-minute artifact-free EEG epochs at 6, 12, 24, 36, 48, 72, 96, and 120 hours after cardiac arrest to be presented to a reviewer.[1] If no epoch was available at these time points, because of artifacts, the closest available artifact-free epoch in the range of ±2 hours was used. EEG reactivity was not routinely tested, and only stimulation-free epochs were used for analysis. Before visual assessment, signals were bandpass filtered (range = 0.5–35Hz). Visual assessment was performed using a longitudinal bipolar montage. EEG epochs were presented in random order to reviewers who were blinded to the timing of the epoch, the clinical condition of the patients, medication, and outcome. All EEG epochs were assessed by 2 experienced reviewers from a pool of 6 (B.J.R., M.C.T.-C., M.J.A.M.v.P., H.K., A.G., or J.H.), independently. If the 2 reviewers disagreed, the final classification was determined by consensus. If necessary, a third reviewer was consulted. Reviewers were allowed to choose the option "No classification possible" if the epoch was considered unreliable due to artifacts. If one of the reviewers chose this option, the epoch was not used for any further analysis.

EEG categorization was based on previous work,[1,7,9] with definitions updated and aligned with the American Clinical Neurophysiology Society standardized critical care EEG terminology to allow for better reproducibility.[17] EEG patterns were classified as generalized suppression (all activity <10 μV), synchronous patterns with ≥50% suppression (generalized periodic discharges on a suppressed background, or burst suppression with generalized, abrupt-onset bursts, with suppressed background and at least 50% of time spent in suppression), continuous (continuous or nearly continuous patterns without periodic activity), or other. Burst suppression with identical bursts,[21] and highly epileptiform bursts typically fulfilled the criteria for "synchronous burst suppression." Spatially heterogeneous burst-suppression patterns were classified as "other patterns." Continuous patterns were subdivided according to their dominant frequency (delta, theta, or ≥alpha). See Figure 1 for examples of synchronous patterns with ≥50% suppression.

Additionally collected data included age, sex, resuscitation details, maximum and cumulative doses of sedative medication, and median nerve SSEP responses. Neuroimaging and biochemical markers were not used in clinical practice.

Outcome

The primary outcome measure was neurological functional recovery at 6 months, expressed as the score on the 5-point Glasgow-Pittsburgh Cerebral Performance Category (CPC),[22] dichotomized as good (CPC = 1 or 2) or poor (CPC = 3, 4, or 5). Outcome was assessed during a standardized telephone interview by 1 of 2 investigators (B.J.R. or M.C.T.-C.) or a trained research nurse. CPC scores were based on a Dutch translation of the EuroQol-6D questionnaire. At 1 center, CPC scores were assessed using the Short Form 36 questionnaire.

Statistical Analysis

To compare patients with good and poor outcomes, categorical variables were analyzed using Pearson χ^2 test, continuous variables using the Mann–Whitney test. Interrater reliability (IRR) for the categorization of EEG patterns was tested using Cohen kappa. Sensitivity and specificity were calculated for EEG predictors of poor or good outcome, including corresponding 95% confidence intervals (CIs). To determine the optimal timing of EEG-based predictions of outcome, we used mixed-effects logistic regression with "patient" as random effects term, to correct for repeated measures of the same patients at different points. We used multivariate logistic regression to assess the additional value of the EEG at 12 hours over the following clinical predictors of outcome: sex, out-of hospital versus in-hospital cardiac arrest, primary cardiac versus noncardiac cause of cardiac arrest, ventricular fibrillation versus other initial cardiac rhythms, hypothermia versus normothermia, and maximum doses of sedative drugs (propofol, midazolam, fentanyl, remifentanil, morphine) in the first 24 hours after cardiac arrest. For the multivariate analysis, we only used data of patients with EEG available at 12 hours. We checked that <10% of data were missing for each clinical predictor. Missing values were estimated using multiple imputation. In case of quasicomplete separation, we used Firth's penalized likelihood approach to estimate model coefficients. For each model, we calculated the area under the curve (AUC) of the receiver operating characteristic curve. CIs of the AUC were calculated using bootstrap samples (n = 2,000). Probability values <0.05 were considered statistically significant. All tests were performed using MATLAB Statistics Toolbox software (MATLAB and Statistics Toolbox Release R2017b; MathWorks, Natick, MA).

Results

Patient Characteristics

Between May 2010 and November 2017, EEG recordings were started in 887 comatose patients after cardiac arrest. Fourteen had no artifact-free EEG at any of the

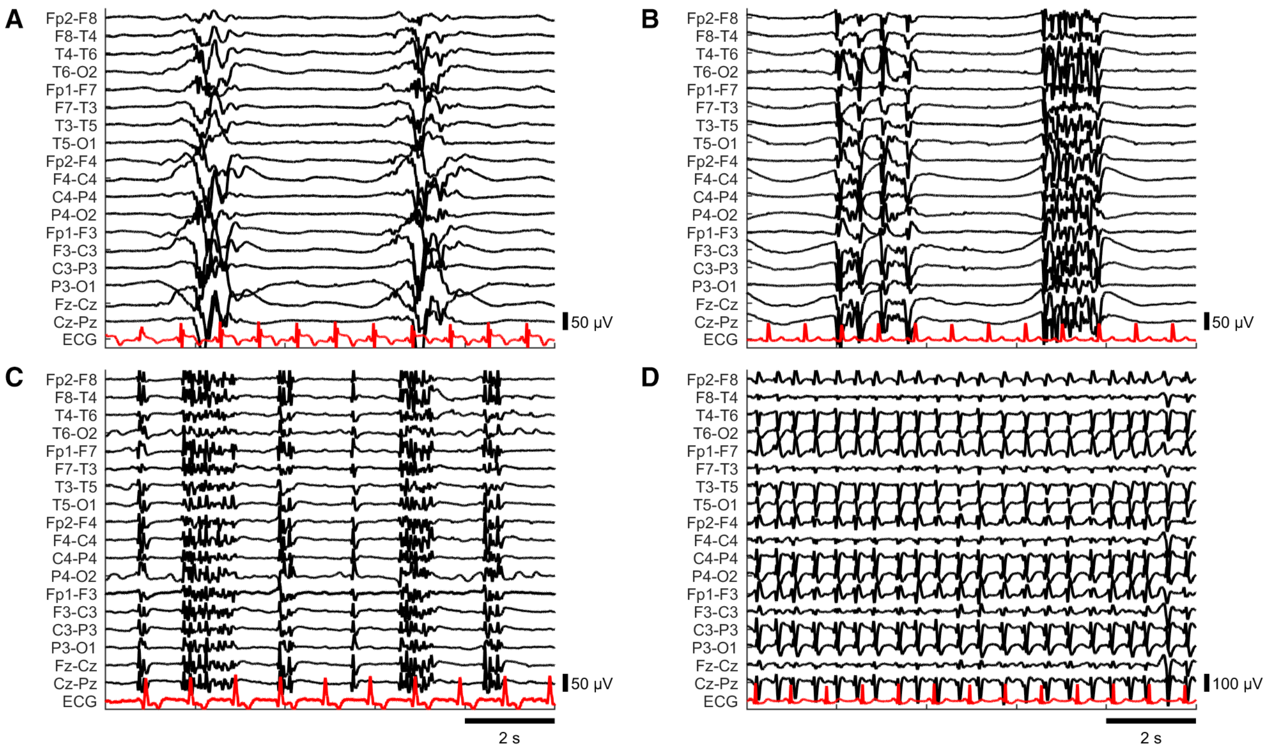


FIGURE 1: Examples of synchronous patterns with ≥50% suppression. (A) Burst suppression with identical bursts. (B) Burst suppression with abrupt-onset, generalized bursts (these bursts could alternatively be described as "highly epileptiform bursts"). (C) Burst suppression with abrupt-onset, generalized bursts, alternating with generalized discharges. (D) Generalized periodic discharges on a suppressed background. [Color figure can be viewed at www.annalsofneurology.org]

investigated time points, and 23 were lost to follow-up, leaving 850 patients for the analyses. We visually assessed a total number of 3,232 EEG epochs. Categorization was impossible for 139 epochs (4%) due to artifacts.

Clinical characteristics are shown in Table 1, grouped by outcome. Poor outcome occurred in 455 patients (54%). As expected, patients with poor outcome were older, more often had a noncardiac cause of arrest, and less often had ventricular fibrillation (VF) as initial rhythm. Patients with a good outcome required higher doses of sedation and analgesia. EEG recordings were stopped earlier in patients with a good outcome (52 vs 62 hours after cardiac arrest), because recordings were terminated at awakening.

Prediction of Poor Outcome

Generalized EEG suppression (all activity <10 μV) and synchronous patterns with ≥50% suppression were invariably associated with a poor outcome, from 6 hours after cardiac arrest onward (Fig 2). Sensitivity for detection of patients with a poor outcome reached its maximum at 12 hours (0.47, 95% CI = 0.42–0.51) and gradually decreased thereafter (Fig 3A, Table 2). At 24 hours, sensitivity was 0.30 (95% CI = 0.26–0.33). Also, after correction for different samples of patients being used to calculate test characteristics at different time points, sensitivity at 12 hours was significantly higher than at later time points (see Fig 3A). Specificity was 100% in all participating centers, despite differences in target temperature and sedative medication, and sensitivity ranged from 0.13 to 0.55 (see Table 2). It should be noted that the center with the lowest sensitivity had only 13 patients with an EEG epoch available at 12 hours.

Prediction of Good Outcome

Continuous EEG patterns were associated with a good outcome, if present within 12 hours after cardiac arrest. At 12 hours, sensitivity was 0.50 (95% CI = 0.46–0.55) at a specificity of 0.91 (95% CI = 0.88–0.93). At later time points, sensitivity increased even further, but at the cost of a lower specificity (see Fig 3B). Specificity of a favorable EEG pattern for prediction of good outcome was not different among participating centers, whereas sensitivity ranged from 0.46 to 0.88 (see Table 2).

Prognostic Value of Other EEG Patterns

For other EEG patterns, the chance of a good outcome was time-dependent. This was most striking for discontinuous patterns (see Fig 2); the chance of a good outcome decreased gradually from 80% at 6 hours to 0% at 120 hours. Likewise, the chance of a good outcome

TABLE 1. Patient Characteristics, Grouped by Outcome

Characteristic	Poor Outcome, CPC = 3–5	Good Outcome, CPC = 1–2	*p*
n	455 (54%)	395 (46%)	
Age, yr	67 (57–75)	60 (51–69)	<0.001
Female	121 (27%)	84 (21%)	0.07
Out-of-hospital cardiac arrest	407 (89%)	367 (93%)	0.08
Noncardiac cause of arrest	94 (24%)	21 (6%)	<0.001
Ventricular fibrillation as initial cardiac rhythm	248 (58%)	352 (91%)	<0.001
Mild therapeutic hypothermia, 33°C	214 (47%)	179 (45%)	0.62
EEG start time, hours after cardiac arrest	11 (6–19)	11 (6–19)	0.70
EEG stop time, hours after cardiac arrest	62 (42–93)	52 (41–78)	0.01
Treatment with propofol	379 (85%)	354 (91%)	0.01
Max dose in first 24 hours, mg/kg/h	2.7 (2.0–3.5)	3.2 (2.4–3.9)	<0.001
Cumulative dose at 24 hours, mg/kg	52 (39–64)	63 (49–77)	<0.001
Treatment with midazolam	124 (28%)	111 (29%)	0.80
Max dose in first 24 hours, μg/kg/h	100 (57–170)	93 (66–153)	0.85
Cumulative dose at 24 hours, mg/kg	0.65 (0.41–1.03)	1.10 (0.51–1.51)	0.04
Treatment with fentanyl	201 (45%)	160 (41%)	0.26
Max dose in first 24 hours, μg/kg/h	1.3 (1.0–1.8)	1.4 (1.1–2.3)	0.03
Cumulative dose at 24 hours, μg/kg	27 (22–38)	32 (25–48)	0.001
Treatment with remifentanil	33 (7%)	21 (5%)	0.24
Max dose in first 24 hours, μg/kg/h	3.6 (2.5–5.6)	6.6 (3.3–11.4)	0.02
Cumulative dose at 24 hours, μg/kg	56 (27–102)	84 (57–166)	0.04
Treatment with morphine	174 (39%)	193 (50%)	<0.001
Max dose in first 24 hours, μg/kg/h	25 (22–31)	25 (21–29)	0.17
Cumulative dose at 24 hours, μg/kg	429 (247–514)	453 (374–527)	0.20
Treatment with sevoflurane	30 (7%)	21 (5%)	0.43
Max end–tidal volume %	1.2 (1.1–1.4)	1.4 (1.2–1.6)	0.03
SSEP performed	276 (61%)	43 (11%)	<0.001
N20 bilaterally absent	123 (27%)	0 (0%)	<0.001

Data are shown as number (percentage) or median (interquartile range).
CPC = Cerebral Performance Category; EEG = electroencephalogram; Max = maximum; SSEP = somatosensory evoked potential.

of heterogeneous burst suppression (ie, not classified as "synchronous pattern with ≥50% suppression") decreased from 37% at 12 hours to 0% at 72 hours and later. All patients with an epileptiform EEG pattern within the first 24 hours, or a low-voltage EEG at 48 hours or later, had a poor outcome.

Prognostic Yield of Continuous EEG Recordings

The chance to identify a poor outcome was highest if EEG recordings were started within 12 hours after cardiac arrest. For subjects with poor outcome who had their first EEG evaluated at 12 hours, the probability of reliable identification of poor outcome was 55%. With

		Time since cardiac arrest							
		6 h (N = 340)	12 h (N = 469)	24 h (N = 742)	36 h (N = 673)	48 h (N = 517)	72 h (N = 298)	96 h (N = 133)	120 h (N = 60)
Supp.	Suppression	0% (0-2) N = 30	0% (0-1) N = 35	0% (0-1) N = 16	0% (0-1) N = 11	0% (0-1) N = 6	0% (0-2) N = 5		
Synchronous ≥ 50% supp.	BS (synchronous)	0% (0-2) N = 32	0% (0-1) N = 77	0% (0-1) N = 79	0% (0-1) N = 40	0% (0-1) N = 18	0% (0-2) N = 7	0% (0-3) N = 1	
	GPDs (supp. bg.)		0% (0-1) N = 1	0% (0-1) N = 15	0% (0-1) N = 24	0% (0-1) N = 23	0% (0-2) N = 7	0% (0-3) N = 8	0% (0-6) N = 6
Continuous	Continuous (delta)	67% (61-72) N = 6	82% (77-86) N = 11	50% (46-54) N = 32	47% (42-51) N = 75	56% (51-61) N = 66	58% (52-64) N = 57	48% (39-58) N = 31	50% (36-64) N = 8
	Continuous (theta)	82% (77-87) N = 17	79% (74-83) N = 71	77% (73-80) N = 222	71% (66-74) N = 272	64% (59-69) N = 214	59% (53-65) N = 93	38% (30-48) N = 26	13% (5-24) N = 16
	Continuous (≥ alpha)	82% (77-87) N = 34	91% (87-94) N = 54	92% (89-94) N = 76	93% (90-95) N = 55	79% (74-82) N = 42	78% (72-83) N = 9	75% (66-82) N = 4	
Other patterns	Low-voltage	19% (14-24) N = 74	16% (13-20) N = 37	0% (0-1) N = 17	10% (7-13) N = 20	0% (0-1) N = 14	0% (0-2) N = 9	0% (0-3) N = 4	0% (0-6) N = 3
	Epileptiform (other)	0% (0-2) N = 2	0% (0-1) N = 4	13% (10-16) N = 16	16% (13-20) N = 55	14% (11-18) N = 69	18% (13-23) N = 61	26% (18-35) N = 27	25% (15-38) N = 12
	BS (heterogeneous)	30% (25-36) N = 43	37% (32-42) N = 57	13% (10-16) N = 40	25% (21-29) N = 12	20% (16-24) N = 5	0% (0-2) N = 2	0% (0-3) N = 3	0% (0-6) N = 1
	Discontinuous	80% (75-85) N = 102	70% (66-75) N = 122	46% (42-50) N = 229	30% (26-34) N = 109	25% (21-29) N = 60	35% (30-42) N = 48	14% (8-21) N = 29	0% (0-6) N = 14

FIGURE 2: Chance of good outcome, given the electroencephalographic (EEG) pattern and its timing after cardiac arrest. In each cell, the percentage indicates the chance of good outcome, the numbers in parentheses the corresponding 95% confidence interval, and N the number of patients with the EEG pattern at the given time. BS = burst suppression; GPD = generalized periodic discharge; Supp. = suppression; supp. bg. = suppressed background pattern. [Color figure can be viewed at www.annalsofneurology.org]

continuous EEG starting between 12 hours and 24 hours, this probability was 36% ($p < 0.001$), and with start time >24 hours it was only 24% ($p < 0.001$).

With repeated EEG evaluation, the proportion of patients in whom reliable prediction of outcome was possible increased (Fig 4). Having at least 1 unfavorable EEG ("suppression" or "synchronous pattern with ≥50% suppression") at 6, 12, or 24 hours after cardiac arrest yielded a sensitivity of 0.52 (95% CI = 0.47–0.58) at a specificity of 1.00 (95% CI = 0.98–1.00). By including the information obtained between 36 hours and 5 days after cardiac arrest, prediction of poor outcome improved only marginally. Sensitivity for good outcome improved by assessment of the EEG at more than one point in time. Because the proportion of patients with continuous EEG patterns and poor outcome also increased over time, this was at the cost of specificity. The presence of at least 1 continuous EEG pattern at 6 hours or 12 hours yielded a sensitivity of 63% (95% CI = 57–68%), at a specificity of 90% (95% CI = 86–93%). The cumulative sensitivity for prediction of good outcome at 120 hours was 98% (95% CI = 96–99%), at a specificity of 69% (95% CI = 64–74%). None of the patients with a continuous EEG at 12 hours had an unfavorable pattern throughout the remainder of the EEG recording.

Interrater Agreement

At 12 hours after cardiac arrest, the interrater reliability was 0.80 (95% CI = 0.74–0.86) for discrimination between continuous and other patterns and 0.78 (95% CI = 0.72–0.85) for discrimination between unfavorable ("suppression" or "synchronous pattern with ≥50% suppression") and other patterns.

Multivariate Models

In the multivariate analysis, an unfavorable EEG at 12 hours after cardiac arrest was an independent predictor of poor outcome (Table 3). Other independent

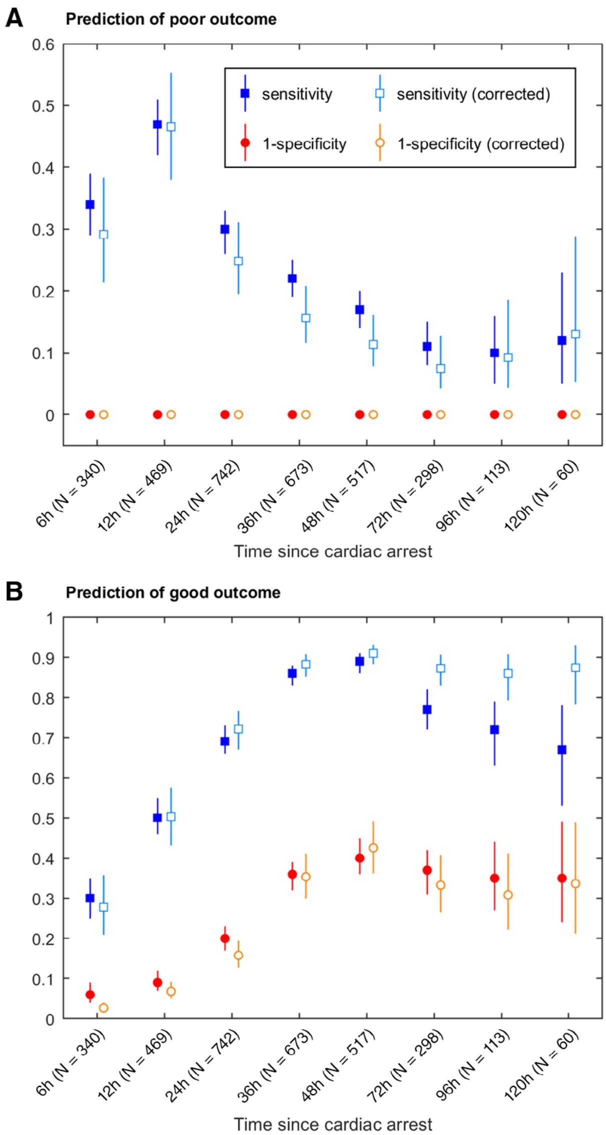


FIGURE 3: Predictive value of the electroencephalogram (EEG) as a function of time after cardiac arrest. "Corrected" values follow from the mixed model, which accounts for the sensitivity and specificity at the 8 time points being calculated from different, partially overlapping groups of patients. Error bars indicate 95% confidence intervals. Numbers (N) refer to the total number of patients with an EEG epoch available at the indicated time point. (A) Test characteristics for the prediction of poor outcome based on "suppression" or "synchronous pattern with ≥50% suppression." (B) Test characteristics for the prediction of good outcome based on "continuous" EEG pattern. [Color figure can be viewed at www.annalsofneurology.org]

predictors of poor outcome were a higher age, a lower maximum dose of propofol in the first 24 hours after cardiac arrest, and not applying hypothermia. The addition of an unfavorable EEG significantly increased the predictive value for poor outcome (AUC = 0.87, 95% CI = 0.83–0.90 vs 0.77, 95% CI = 0.72–0.81; Fig 5A). Likewise, a favorable EEG at 12 hours after cardiac arrest was an independent predictor of good outcome (see Table 3). Other independent predictors of good outcome were a lower age, and higher maximum doses of propofol and fentanyl in the first 24 hours after cardiac arrest. The addition of a favorable EEG significantly increased the predictive value for good outcome (AUC = 0.84, 95% CI = 0.81–0.88 vs 0.77, 95% CI = 0.72–0.81; see Fig 5B).

In combination, SSEP and early EEG identified more patients with a poor outcome than EEG alone. Of those with EEG available within the first 24 hours after cardiac arrest, an unfavorable pattern ("suppression" or "synchronous pattern with ≥50% suppression") at 6, 12, or 24 hours identified 181 of 420 (43%) patients with a poor outcome. In the same group, absent SSEP responses allowed for reliable prediction of outcome in an additional 31 patients (7%).

Discussion

With this prospective cohort study, including 850 patients from 5 hospitals, we confirm that early EEG allows for reliable prediction of outcome of comatose patients after cardiac arrest. Generalized suppression or synchronous patterns with at least 50% suppression were invariably associated with a poor outcome between 6 hours and 5 days after cardiac arrest. A continuous background pattern at 6 or 12 hours was an independent predictor of good outcome. Predictive values were highest at 12 to 24 hours after cardiac arrest. Predictors were equally specific among 5 centers, despite differences in target temperature or sedative medication. We confirm that unfavorable EEG patterns and absent SSEP responses have complementary value for the prediction of poor outcome.

Context of Previous Work

Our results validate previous findings on reliability and time dependency of EEG patterns.[1] The achieved improvement of sensitivity for reliable prediction of poor outcome, from 0.29 to 0.47, was achieved by lumping previously identified unfavorable EEG categories[1,7,19] and by aligning definitions with standardized terminology. Studies reporting higher sensitivities were either retrospective, inheriting the risk of selection bias,[7,8] or not without false positives.[2] Studies showing conflicting results did not account for time dependency.[5] In line with international terminology,[17] we now used a suppressed background pattern (indicating ≤10 μV) as hallmark. The previously reported low-voltage criterion (indicating ≤20 μV) EEG was not 100% specific for the prediction of poor outcome, as 2 patients with low-voltage patterns at 36 hours eventually recovered. One group reported a few cases that recovered despite a

TABLE 2. Comparison of Treatment and Predictive Values of Electroencephalography between Centers

	Center 1	Center 2	Center 3	Center 4	Center 5	All
Recruitment period	May 2010–Nov 2017	Jun 2012–Oct 2017	Jul 2015–Oct 2017	Oct 2014–Aug 2017	Feb 2016–Nov 2017	May 2010–Nov 2017
Subjects, n	351	272	93	67	67	850
Medication, ≤24h after CA						
Propofol	343 (98%)	222 (86%)	92 (99%)	66 (99%)	7 (10%)	730 (86%)
Midazolam	70 (20%)	136 (53%)	2 (2%)	13 (19%)	16 (24%)	237 (28%)
Sevoflurane	0 (0%)	0 (0%)	0 (0%)	0 (0%)	51 (76%)	51 (6%)
Morphine	3 (1%)	248 (96%)	76 (82%)	39 (58%)	0 (0%)	366 (43%)
Fentanyl	294 (84%)	0 (0%)	0 (0%)	2 (3%)	63 (94%)	359 (42%)
Remifentanil	45 (13%)	1 (0%)	8 (9%)	0 (0%)	0 (0%)	54 (6%)
Hypothermia, 33°C	311 (89%)	75 (28%)	0 (0%)	0 (0%)	7 (10%)	393 (46%)
Prediction of poor outcome, 12 hours after CA						
Sensitivity (95% CI)	0.55 (0.48–0.61)	0.42 (0.34–0.51)	0.43 (0.28–0.59)	0.13 (0.01–0.42)	0.36 (0.22–0.51)	0.47 (0.42–0.51)
Specificity (95% CI)	1.00 (0.98–1.00)	1.00 (0.96–1.00)	1.00 (0.89–1.00)	1.00 (0.70–1.00)	1.00 (0.90–1.00)	1.00 (0.99–1.00)
Prediction of good outcome, 12 hours after CA						
Sensitivity (95% CI)	0.46 (0.39–0.52)	0.46 (0.37–0.54)	0.56 (0.39–0.71)	0.75 (0.43–0.95)	0.88 (0.74–0.96)	0.50 (0.46–0.55)
Specificity (95% CI)	0.94 (0.90–0.97)	0.84 (0.77–0.90)	0.95 (0.82–1.00)	0.88 (0.55–1.00)	0.89 (0.76–0.97)	0.91 (0.88–0.93)

Values are shown per center and for the overall cohort (All). Prediction of poor outcome was based on the presence of an unfavorable pattern (generalized suppression or synchronous pattern with ≥50% suppression). Prediction of good outcome was based on the presence of a continuous pattern.
CA = cardiac arrest; CI = confidence interval.

suppressed EEG at 12 or 24 hours after cardiac arrest, but in their definition recovery of consciousness was sufficient for "good outcome."[8]

Yield of Continuous EEG Monitoring

We show that repeated assessment of the EEG within the first 24 hours after cardiac arrest improves the sensitivity for reliable detection of either good or poor outcome. These results contradict findings of a smaller study, which concluded that continuous EEG does not have additional value over routine spot EEGs during hypothermia.[23] However, this previous work did not account for evolution of the EEG during the first 24 hours after cardiac arrest. With the current study, the prognostic yield of prolonging continuous EEG beyond 24 hours was limited. However, diagnosis of epileptiform patterns, which might warrant treatment, was not taken into account.

Specific Predictors of Poor Outcome

We confirm the reliability for the prediction of poor outcome of "synchronous patterns with ≥50% suppression." One of its subgroups is burst suppression with abrupt-onset, generalized bursts on a suppressed background, with at least 50% of the record consisting of suppression. Sixty-five percent of these patterns showed identical bursts.[21] The second subgroup is generalized periodic discharges on a suppressed background.[7,9,16] These results are in line with findings of our recent quantitative analysis, in which we showed that an amplitude ratio between nonsuppressed and suppressed segments of ≥6.12 is invariably associated with a poor outcome.[19]

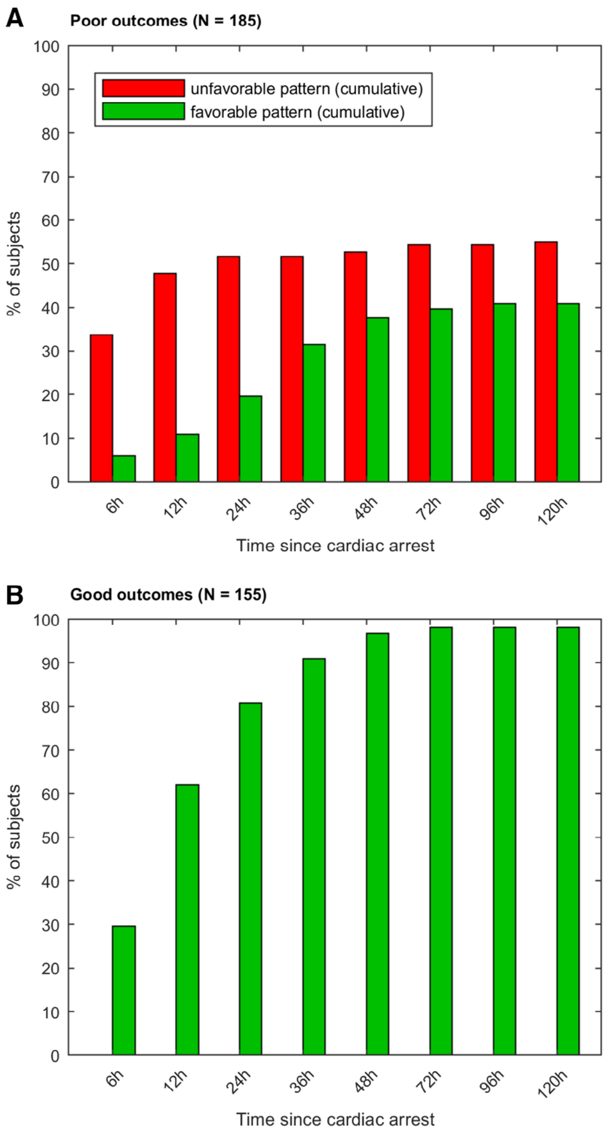


FIGURE 4: Prognostic yield of repeated electroencephalographic (EEG) assessment. This analysis includes only patients with an EEG recording started within 6 hours after cardiac arrest. Bars indicate the fraction of subjects in whom an unfavorable ("suppression" or "synchronous pattern with ≥50% suppression") or favorable EEG pattern ("continuous") was observed up to the indicated time point, respectively. (A) Results for all 185 patients with poor outcome. (B) Results for all 155 patients with good outcome. [Color figure can be viewed at www.annalsofneurology.org]

Some authors have claimed that all burst-suppression patterns predict a poor outcome, regardless of the burst type.[7,9,10,24] This was typically with studies starting >72 hours after cardiac arrest.[9,10] One study that included burst suppression as predictor of poor outcome in early EEG, and did not specify burst types, was not without false positives.[2]

EEG Background Reactivity

We only investigated spontaneous EEG patterns and did not assess background reactivity of the EEG. The presence of reactivity seems very sensitive for prediction of a good outcome, but lacks specificity to make relevant predictions of outcome.[2] Results on absent reactivity for the prediction of poor outcome are conflicting,[2,7–9,12] most likely resulting from a lack of standardization of stimulus protocols and quantitative definitions of reactivity.[25] Studies on the additional value of reactivity over background EEG pattern for prediction of outcome after cardiac arrest are lacking.

EEG interpretation in this study may have been influenced by the use of sedative medication, with the risk of falsely pessimistic predictions of outcome. However, recent studies show that the effects of sedation on the EEG are small compared to those of anoxic encephalopathy.[26,27] In line with this, our multivariate analysis shows that higher doses of propofol and fentanyl are independent predictors of good instead of poor outcome.

Limitations

Although this study meets Standards for the Reporting of Diagnostic Accuracy Studies criteria (www.stard-statement.org), it has limitations. Like almost all studies on prognostication of comatose patients after cardiac arrest, we cannot exclude the potential bias of self-fulfilling prophecy.[28] To minimize this risk, decisions on treatment withdrawal were based on international guidelines including bilaterally absent SSEP, absent or extensor motor responses, and absent brainstem reflexes.[3] EEG recordings were intended for the detection and treatment of electrographic seizures, and none of the participating centers used recommendations to withdraw care based on early EEG findings. The only way to mitigate the bias of self-fulfilling prophecies entirely would be to employ a protocol that prohibits early withdrawal of care, for example for at least 2 weeks after cardiac arrest. In the Netherlands, however, such a study protocol would not be possible due to prevailing ethical norms.

As a second limitation, outcome for some of the patients may have been influenced by causes unrelated to the postanoxic encephalopathy. Because we aimed for a realistic patient sample, not biased by selection, we did not exclude patients who died from other organ failure, such as a second cardiac arrest. This may have limited the specificity of our predictions of good outcome.

Finally, visual assessment of EEG is subject to interrater variability. Nevertheless, the interrater reliability for the distinction between unfavorable (generalized suppression or synchronous patterns with >50% suppression) or favorable (continuous) EEG patterns and other patterns

TABLE 3. Multivariate Models

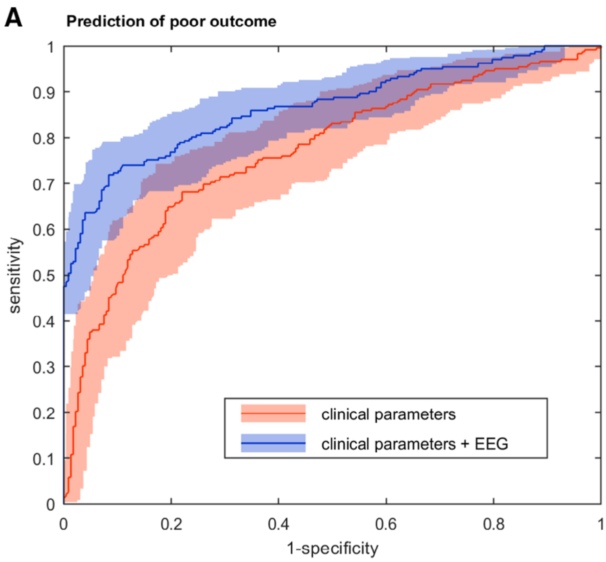
	Full Model B (SE)	p	Reduced Model B (SE)	p
Prediction of poor outcome[a]				
Intercept	−1.032 (0.839)	0.21	−1.051 (0.716)	0.14
Age	0.039 (0.010)	<0.001	0.040 (0.010)	<0.001
Female	0.000 (0.300)	1.00		
Out-of-hospital cardiac arrest	−0.159 (0.410)	0.69		
Noncardiac cause of arrest	0.311 (0.436)	0.47		
VF as initial cardiac rhythm	−1.432 (0.363)	<0.001	−1.547 (0.312)	<0.001
Mild therapeutic hypothermia, 33°C	−0.389 (0.298)	0.19	−0.509 (0.266)	0.06
Propofol dose, mg/kg/h	−0.181 (0.094)	0.05	−0.178 (0.083)	0.03
Midazolam dose, μg/kg/h	−0.001 (0.003)	0.79		
Fentanyl dose, μg/kg/h	−0.084 (0.186)	0.65		
Remifentanil dose, μg/kg/h	0.005 (0.080)	0.95		
Morphine dose, μg/kg/h	0.008 (0.012)	0.51		
Unfavorable EEG at 12 hours	5.922 (1.400)	<0.001	5.957 (1.428)	<0.001
Favorable EEG at 12 hours	N.A.	N.A.	N.A.	N.A.
Prediction of good outcome[b]				
Intercept	−1.644 (0.862)	0.06	−1.602 (0.680)	0.02
Age	−0.028 (0.009)	0.003	−0.027 (0.009)	0.002
Female	0.177 (0.287)	0.54		
Out-of-hospital cardiac arrest	0.111 (0.435)	0.80		
Noncardiac cause of arrest	−0.560 (0.404)	0.17		
VF as initial cardiac rhythm	1.871 (0.358)	<0.001	2.130 (0.312)	<0.001
Mild therapeutic hypothermia, 33°C	0.216 (0.285)	0.45		
Propofol dose, mg/kg/h	0.333 (0.089)	<0.001	0.311 (0.083)	<0.001
Midazolam dose, μg/kg/h	0.001 (0.002)	0.56		
Fentanyl dose, μg/kg/h	0.194 (0.171)	0.26	0.221 (0.128)	0.09
Remifentanil dose, μg/kg/h	0.003 (0.084)	0.97		
Morphine dose, μg/kg/h	−0.002 (0.011)	0.85		
Unfavorable EEG at 12 hours	N.A.	N.A.	N.A.	N.A.
Favorable EEG at 12 hours	2.531 (0.314)	<0.001	2.484 (0.304)	<0.001

Multivariate models for prediction of outcome. Doses of anesthetic drugs refer to the maximum doses within the first 24 hours after cardiac arrest.

[a]For the prediction of poor outcome, the difference in AUC of the ROC curve between the full model (0.87, 95% CI = 0.83–0.90) and the reduced model (0.87, 95% CI = 0.83–0.90) was not statistically significant.

[b]For the prediction of good outcome, the difference in AUC of the ROC curve between the full model (0.85, 95% CI = 0.81–0.88) and the reduced model (0.84, 95% CI = 0.81–0.88) was not statistically significant. ROC curves indicating the performance of the reduced models are shown in Figure 5.

AUC = area under the curve; B = model coefficient; CI = confidence interval; EEG = electroencephalogram; N.A. = not applicable; ROC = receiver operating characteristic; SE = standard error; VF = ventricular fibrillation.



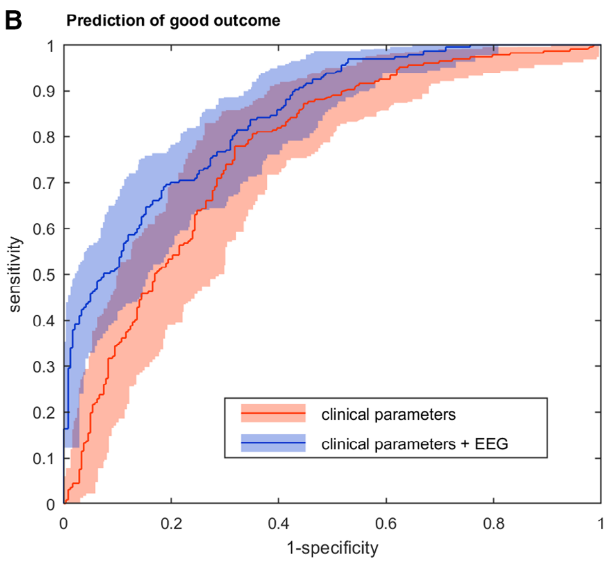


FIGURE 5: Receiver operating characteristic (ROC) curves for multivariate models. Solid lines indicate ROC curves, lighter areas the corresponding 95% confidence intervals. Each subfigure shows results for the model without electroencephalography (EEG) and the model including EEG. Details for models that include EEG are shown in Table 3. (A) Models for prediction of poor outcome. Clinical parameters include age, initial cardiac rhythm (ventricular fibrillation [VF] or other), maximum dose of propofol in the first 24 hours after cardiac arrest, and the application of hypothermia (yes or no). (B) Models for prediction of good outcome. Clinical parameters include age, initial cardiac rhythm (VF or other), and maximum doses of propofol and fentanyl in the first 24 hours after cardiac arrest. [Color figure can be viewed at www.annalsofneurology.org]

was good (IRR = 0.78–0.80), and better than those reported for absent SSEP responses (IRR = 0.20–0.76).[29,30]

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Author Contributions

B.J.R., M.C.T.-C., M.J.A.M.v.P., and J.H. contributed to the conception and the design of the study; all authors contributed to the acquisition and analysis of the data; B.J.R. was responsible for the statistical analysis, writing of the first draft, and preparing the figures; all authors contributed to revising the manuscript.

Potential Conflicts of Interest

M.J.A.M.v.P. is cofounder of Clinical Science Systems, a supplier of EEG systems that have been used to collect study data at Medical Spectrum Twente. The other authors declare that they have no competing interests.

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